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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,229	10/06/2008	Peter Vollmers	50274/021003	1348

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EXAMINER	
HALVORSON, MARK	
ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
03/18/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/586,229	VOLLMERS ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-10,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/9/2008;9/19/2008* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 5-10, 13 and 14 are pending and under consideration.

Drawings

The drawings are objected to because Figure 16 is not labeled. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an isolated polypeptide that specifically binds to a neoplastic cell or a cell of a pre-cancerous lesion, but does not specifically bind to a normal cell, wherein said isolated polypeptide comprises amino acids 28-32, 51-53, and 90-100 of the sequence of SEQ ID NO:29. Thus, the claims read on a polypeptide that does not include all 6 CDRs.

The specification discloses that the CFR-1 isoform recognized by PAM-1 antibody binds to esophagus, stomach, colon cervical, breast and prostate pre cancerous tissues. (Table 3). The antibody, PAM-1 comprises SEQ ID NOs: 28 and 29. (Figs. 17, 18 of the present application). The specification discloses that fragmented PAM-1 induces the apoptosis of the human gastric adenocarcinoma cell line 23132/87 *in vitro*. (page 68, line21 to page 69, line 2). The specification also disclose that fragmented PAM-1 antibody decreased tumor growth of the human gastric adenocarcinoma cell line 23132/87 *in vivo*. (page 69, lines 4-15). The specification does not disclose that a PAM-1 antibody that does not include all 6 CDRs was effective in inhibiting tumor growth. The specification also doses not disclose any other polypeptide besides an antibody that treats a proliferative disorder.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper

association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Colman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum et al (J. Mol. Biol., 262, 732-745, 1996) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col.) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al (Biochemical and Biophysical Research Communications, 2003, Vol. 307, pp. 198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.).

It is unlikely that antibodies, which do not contain all of the specific heavy and light chain CDRs of the PAM-1 antibody in their proper order and in the context of

framework sequences, which maintain their correct spatial orientation, have the requisite binding function. The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibodies with only one identified heavy chain (SEQ ID NO:28) or a polypeptide with only one identified light chain (SEQ ID NO:29), or an antibody with less than the 6 CDRs, wherein the antibodies are capable of treating a proliferative disorder.

In addition, the polypeptide recited in claim 2 does not necessarily bind to the cells recited in claim 1 for the following reasons: As indicated by Paul above, amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. A "polypeptide" is a molecular chain of amino acids.

The specification does not teach any other polypeptide structure other than an antibody that comprises amino acids 28-32, 51-53, and 90-100 of the sequence of SEQ ID NO:29 and further comprises amino acids 11-18, 36-43, and 82-104 of the sequence of SEQ ID NO:28 that binds to a neoplastic cell. A polypeptide does not necessarily comprise the required conformation having the proper antigen binding site of an antibody, and thus does not necessarily bind a neoplastic cell.

Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. The scope of the claims must bear a reasonable correlation with the scope of enablement.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, Coleman P. M., MacCallum et al and Casset et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed antibodies comprising fewer than all six CDRs from the antibody, PAM-1, that would treat a proliferative disorder in a mammal with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibodies and absent working examples providing evidence which is reasonably predictive that the claimed antibodies comprising fewer than all six CDRs identified from the antibody, PAM-1, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5-10, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vollmers et al (Cancer, 1994, 74:1525-32, IDS) as evidenced by Brandlein (Human Antibodies, 2002, 107-119, IDS) in view of Robinson et al (U.S. Patent 5,618,920, filed 4/94).

The claims are drawn to an isolated polypeptide that specifically binds to a neoplastic cell or a cell of a pre-cancerous lesion, but does not specifically bind to a normal cell, wherein said isolated polypeptide comprises amino acids 28-32, 51-53, and 90-100 of the sequence of SEQ ID NO:29, wherein binding of said purified polypeptide results in the induction of apoptosis of the cell, wherein said proliferative disorder is tumors of the stomach, wherein said polypeptide is a functional fragment of an antibody selected from the group consisting of V.sub.L, V.sub.H, F.sub.V, F.sub.C, Fab, Fab', and F(ab').sub. The claims are also drawn to an isolated nucleic acid molecule comprising nucleic acids 31-54, 106-129, and 244-312 of the sequence of SEQ ID NO:26, and/or 82-96, 151-159, and or 268-300 of the sequence of SEQ ID NO:27 and a vector comprising the nucleic acid sequence of SEQ ID NO:26, or SEQ ID NO:27.

Vollmers et al disclose an antibody 103/51 that binds to tumor antigens

expressed on gastric adenomcarcinoma cell lines page 1528, Table 2). As evidenced by Brandlein, antibody 103/51 is Pam-1 (page 108, 1st column). The antibody, PAM-1 comprises SEQ ID NOs: 28 and 29. and is encoded by the nucleic acids of SEQ ID NOs:26 and 27. (Figs. 17, 18 of the present application)

Vollmers et al does not disclose an antibody comprising the sequence of SEQ ID NO:28 and SEQ ID NO:29 that is encoded by the nucleic acid sequence of SEQ ID NO:26, and SEQ ID NO:27.

Robinson et al teach the determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce recombinant antibodies (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Robinson et al further disclose the use of Kabat to determine the variable region domains. (Example III). Robinson et al also disclose antibody fragments such as Fab fragments (column 5, lines 4-8).

One of ordinary skill in the art would have been motivated to apply Robinson et al's method determination of nucleic acids encoding VH and VL of an antibody to Vollmers et al PAM-1 antibody because Robinson et al states teach the determination of nucleic acids encoding VH and VL of any known antibody while Vollmers et al disclose that the antigen recognized by PAM-1 is present on gastric adencarcinomas. It would have been prima facie obvious to combine Vollmers et al PAM-1 antibody with Robinson et al's method determination of nucleic acids encoding VH and VL of an antibody to make nucleic acid molecules comprising SEQ ID NOs: 26 and 27 and an antibody comprising the amino acid sequences of SEQ ID NO:28 and 29.

Neither Vollmers et al nor Robinson et al disclose an antibody that induces apoptosis. However, the antibody of Vollmers et al and Robinson et al would inherently induce apoptosis. The rejection based on inherency is based on the property that the PAM-1 antibody induces the apoptosis of tumor cells..

According to MPEP 2112

> "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not
> necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Furthermore, as indicated in MPEP 2112

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

The antibody of Vollmers et al and Robinson et al would inherently induce apoptosis of the gastric adenocarcinoma cell.

Summary

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

/Mark Halvorson/
Examiner, Art Unit 1642